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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,517	12/06/1999	BRADFORD J DUFT	030639.0044.CPA1	1018

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Intellectual Property Department
Amylin Pharmaceuticals, Inc.
9360 Towne Centre Drive
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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	PAPER NUMBER
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/445,517	DUFT ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-29,31-39,68-80,82 and 84-97* is/are pending in the application.

4a) Of the above claim(s) *25, 26, 28, 35, 36, 69-71, 73-75, 77-79 and 85-94* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,24,27,29,31-34,37-39,68,72,76,80,82 and 84-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

REQUEST FOR CONTINUED EXAMINATION

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 11/30/06 has been entered.

Applicants' Amendment

2) Acknowledgment is made of Applicants' amendment filed 11/30/06 in response to the final Office Action mailed 05/30/06. With this, Applicants have amended the claims.

Status of Claims

3) Claims 30, 81 and 83 have been canceled via the amendment filed 11/30/06.

Claims 23, 27, 29, 31-34, 37-39, 68, 72, 76 and 80 have been amended via the amendment filed 11/30/06.

New claims 95-97 have been added via the amendment filed 11/30/06.

Claims 23-29, 31-39, 68-80, 82 and 84-97 are pending.

Claims 23, 24, 27, 29, 31-34, 37-39, 68, 72, 76, 80, 82 and 84-97 are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

6) The objection to the specification made in paragraph 8 of the Office Action mailed 05/30/06 is withdrawn in light of Applicants' amendment to claim 33.

Rejection(s) Moot

7) The rejection of claims 30, 81 and 83 made in paragraph 34 of the Office Action mailed 05/30/06 under 35 U.S.C § 112, first paragraph, as containing new subject matter, is moot in light of Applicants' cancellation of the claims.

8) The rejection of claim 83 made in paragraph 35 of the Office Action mailed 05/30/06 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is moot in light of Applicants' cancellation of the claim.

9) The rejection of claim 30 made in paragraph 36(a) of the Office Action mailed 05/30/06 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

10) The rejection of claims 81 and 83 made in paragraph 36(e) of the Office Action mailed 05/30/06 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

11) The rejection of claims 30 and 81 made in paragraph 38 of the Office Action mailed 05/30/06 under 35 U.S.C § 102(e)(2) as being anticipated by Beeley *et al.* (US 6,956,026, filed 01/07/1997), is moot in light of Applicants' cancellation of the claims.

12) The rejection of claims 30 and 81 made in paragraph 39 of the Office Action mailed 05/30/06 under 35 U.S.C § 102(b) as being anticipated by Thompson *et al.* (*Diabetes* 46: Suppl. 1, page 30A, 0116, 02 May 1997, already of record) (Thompson *et al.*, May, 1997), is moot in light of Applicants' cancellation of the claims.

13) The rejection of claims 30 and 81 made in paragraph 40 of the Office Action mailed 05/30/06 under 35 U.S.C § 102(b) as being anticipated by Thompson *et al.* (*Diabetologia* 40: 1278-1285, November 1997, already of record) (Thompson *et al.*, November, 1997), is moot in light of Applicants' cancellation of the claims.

14) The rejection of claims 30 and 81 made in paragraph 41 of the Office Action mailed 05/30/06 under 35 U.S.C § 102(b) as being anticipated by Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996, already of record) (Kolterman *et al.*, 1996), is moot in light of Applicants'

cancellation of the claims.

Rejection(s) Withdrawn

15) The rejection of claims 33, 34 and 82 made in paragraph 27 of the Office Action mailed 05/30/06 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 64 and 68 of the US patent 6,956,026 (Beeley *et al.*, '026, filed 01/07/1997), is withdrawn in light of Applicants' amendment to the claims.

16) The rejection of claims 23, 24, 33 and 34 made in paragraph 29 of the Office Action mailed 05/30/06 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 34 and 35 of the US patent 5,686,411 issued to Gaeta *et al.* (already of record) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract), is withdrawn in light of Applicants' amendment to the claims. A modified/new rejection is set forth below to reject the claims as amended currently. Applicants' arguments with respect to the rejection have been considered but are moot in view of the modified/new rejection set forth below. Applicants' acknowledgment that obesity is common among those with diabetes has been noted.

17) The rejection of claims 23 and 33 made in paragraph 30 of the Office Action mailed 05/30/06 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11 and 13 of the US patent 5,321,008 issued to Beaumont *et al.* (already of record) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract) and Rink *et al.* (US 5,739,106, already of record) ('106), is withdrawn in light of Applicants' amendment to the claims. A modified/new rejection is set forth below to reject the claims as amended currently. Applicants' arguments with respect to the rejection have been considered but are moot in view of the modified/new rejection set forth below. Applicants' acknowledgment that obesity is common among those with diabetes has been noted.

18) The rejection of claims 23, 76 and dependent claims 24, 27, 29-32, 68, 80, 83 and 84 made in paragraph 31 of the Office Action mailed 05/30/06 under 35 U.S.C § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' amendment to the claims.

19) The rejection of claim 32 made in paragraph 32 of the Office Action mailed 05/30/06 under 35 U.S.C § 112, first paragraph, as containing new subject matter, is withdrawn in light of

Applicants' amendment to the claim.

20) The rejection of claim 33 and dependent claims 34, 37-39, 72 and 82 made in paragraph 33 of the Office Action mailed 05/30/06 under 35 U.S.C § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' amendment to the claim.

21) The rejection of claims 24, 27, 29, 31 and 32 made in paragraph 36(a) of the Office Action mailed 05/30/06 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

22) The rejection of claims 34 and 37-39 made in paragraph 36(b) of the Office Action mailed 05/30/06 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

23) The rejection of claim 33 made in paragraph 36(c) of the Office Action mailed 05/30/06 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

24) The rejection of claims 68, 72 and 76 made in paragraph 36(d) of the Office Action mailed 05/30/06 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

25) The rejection of claims 34, 37-39, 68, 72, 82 and 84 made in paragraph 36(e) of the Office Action mailed 05/30/06 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

26) The rejection of claims 23, 24, 27, 29, 33, 34, 37, 38, 80 and 82 made in paragraph 38 of the Office Action mailed 05/30/06 under 35 U.S.C § 102(e)(2) as being anticipated by Beeley *et al.* (US 6,956,026, filed 01/07/1997), is withdrawn in light of Applicants' amendment to the claims.

27) The rejection of claims 23, 24, 29, 33, 34, 37, 38, 80 and 82 made in paragraph 39 of the Office Action mailed 05/30/06 under 35 U.S.C § 102(b) as being anticipated by Thompson *et al.* (*Diabetes* 46: Suppl. 1, page 30A, 0116, 02 May 1997, already of record) (Thompson *et al.*, May, 1997), is withdrawn in light of Applicants' amendment to the claims and/or the base

claim(s).

28) The rejection of claims 23, 24, 29, 31, 33, 34, 37-39, 80 and 82 made in paragraph 40 of the Office Action mailed 05/30/06 under 35 U.S.C § 102(b) as being anticipated by Thompson *et al.* (*Diabetologia* 40: 1278-1285, November 1997, already of record) (Thompson *et al.*, November, 1997), is withdrawn in light of Applicants' amendment to the claims and/or the base claim(s).

29) The rejection of claims 23, 24, 29, 31, 33, 34, 37-39, 80 and 82 made in paragraph 41 of the Office Action mailed 05/30/06 under 35 U.S.C § 102(b) as being anticipated by Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996, already of record) (Kolterman *et al.*, 1996), is withdrawn in light of Applicants' amendments to the claims and/or the base claims. A modified/new rejection is set forth herein below to address the claims as amended. Applicants' arguments with respect to the rejection have been considered but are moot in view of the modified/new rejection set forth below.

30) The rejection of claims 23, 24, 27, 29, 31, 33, 34, 37-39, 80 and 82 made in paragraph 42 of the Office Action mailed 05/30/06 under 35 U.S.C § 102(b) as being anticipated by Kolterman *et al.* (WO 96/40220, already of record) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract), is withdrawn in light of Applicants' amendments to the claims and/or the base claims. A modified/new rejection is set forth herein below to address the claims as amended. Applicants' acknowledgment that obesity is indeed a common characteristic of patients with type II diabetes mellitus has been noted.

Rejection(s) Maintained

31) The provisional rejection of the instant claims made in paragraph 26 of the Office Action mailed 05/30/06 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of the co-pending application, SN 09/870,762, is maintained for reasons set forth therein. Applicants' statement that they are willing to consider submitting a terminal disclaimer in the present application with regard to the '762 application should this application issue as a patent prior to the present application, has been noted.

32) The provisional rejection of claims 33 and 82 made in paragraph 28 of the Office Action

mailed 05/30/06 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 6 of the co-pending application, 10/851,574, is maintained for reasons set forth therein. Applicants' statement that they are willing to consider submitting a terminal disclaimer in the present application with regard to the '574 application should this application issue as a patent prior to the present application has been noted.

33) The rejection of claims 68, 72, 76 and 84 made in paragraph 35 of the Office Action mailed 05/30/06 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is maintained for reasons set forth therein and herein below.

New dependent claim 97 is now added to this rejection.

Applicants contend that amylin agonist analogues comprising SEQ ID NO: 14 for use in the present invention are described in the specification and well known in the art. Applicants state that pages 40, 41 and 46 of the specification provide representative examples of amylin agonist analogues comprising SEQ ID NO: 14 for use in the claimed invention. Applicants submit that amylin agonist analogues comprising SEQ ID NO: 14 were also known in the art at the time the present application was filed and that such analogues were include those described in US patent 5,686,411 as described in the present specification at page 13, lines 23-28 and those described in US 6,114,304, of record. Applicants state that these amylin agonist analogues have been shown to mimic an effect of amylin *in vitro* or *in vivo*. Applicants submit that as shown in Examples 7-9 of the present specification, many of these amylin agonist analogues possess amylin activity (receptor binding or muscle assay) comparable to that of human amylin and to that of pramlintide. Applicants contend that the conventional assays for identifying amylin agonist analogues and for detecting amylin activity of compounds comprising SEQ ID NO: 14 are described in the specification and are known in the art. Applicants state that the specification at page 19, line 6 to page 24, line 15, describes how to make amylin analogues and how to assess the compounds for amylin activity and that Examples 1-3 of the specification describe how to assess the compounds for activity in treating obesity. Applicants further submit that the amylin agonist analogue of SEQ ID NO: 14 does not permit any and all amino acid substitutions at any and all amino acid positions of amylin. Applicants state that the amino acid substitutions defined in SEQ ID NO: 14 are limited to only specific amino acid substitutions at only particular amino acid positions of amylin.

Applicants contend that the specification demonstrates that many species of amylin analogues that fall within the genus of SEQ ID NO: 14 have activities comparable to native amylin and to pramlintide. Applicants cite *In re Wands* and state that the test for enablement is not whether a certain amount of experimentation is required to practice an invention, but rather whether the amount of experimentation is 'undue'. Applicants cite case law and state that since one embodiment .... is disclosed in the specification, along with the general manner in which its current range was ascertained, ... other permutations of the invention could be practiced by those skilled in the art without undue experimentation. Applicants

Applicants' arguments have been carefully considered, but are not persuasive. As amended, the claimed method is of treating obesity in any human subject comprising or consisting of administering to said subject a composition comprising any peptide or any amylin agonist analogue comprising the amino acid sequence of SEQ ID NO: 14 as recited, wherein A1 is Lys, Ala, Ser, or hydrogen; B1 is Ala, Ser or Thr; C1 is Val, Leu or Ile; D1 is His or Arg; E1 is Ser or Thr; F1 is Ser, Thr, Gln, or Asn; G1 is Asn, Gln or His; H1 is Phe, Leu or Tyr; I1 is Ile, Val, Ala or Leu; J1 is Ser, Pro or Thr; K1 is Asn, Asp or Gln; X and Y are independently selected residues having side chains which are chemically bonded to each other to form an intramolecular linkage, wherein said intramolecular linkage comprises a disulfide bond, a lactam or a thioether linkage; and Z is an amino, alylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, alkyloxy, aryloxy or aralkyloxy; and provided that when A1 is Lys, B1 is Ala, C1 is Val, D1 is Arg, E1 is Ser, F1 is Ser, G1 is Asn, H1 is Leu, I1 is Val, J1 is Pro, and K1 is Asn; then one or more A to K1 is a D-amino acid and Z is selected from the group consisting of alkylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, alkyloxy, aryloxy or aralkyloxy, or such a composition. In the method claimed in claims 68 and 76, the composition is not administered in conjunction with another obesity relief agent. In the method claimed in claims 68 and 72, the amount of the amylin agonist analogue administered is about 0.01 mg to about 5 mg per day.

As set forth previously, the genus 'human subject in need thereof' encompasses within its scope diabetic and non-diabetic humans, morbidly and non-morbidly obese humans etc. The amylin agonist analogue or the peptide of the recited structure of SEQ ID NO: 14 encompasses a large number of amylin agonist analogue or peptide variant subsequence species. Each of the

species, or a representative number of the species encompassed within the scope of the instantly claimed method is *required* to be effective in treating obesity in a diabetic or non-diabetic human subject, or a morbidly or non-morbidly obese human subject when administered not in conjunction with another obesity relief agent in the recited dose range. However, neither the art at the time of the invention, nor the instant specification demonstrates the obesity-treating function(s) of these peptide variant or amylin agonist analogue species in a diabetic or non-diabetic human in need of treatment of obesity on administration by any route for any length of time. Whether or not many species of amylin agonist analogues, which fall within the genus of SEQ ID NO: 14, are known in the art or mentioned in the instant specification, and whether or not the conventional assays for identifying amylin agonist analogues and for detecting amylin activity, are known in the art or described in the specification, is not the issue. Whether or not the amylin agonist analogues mentioned in the specification or known in the art have been shown to mimic 'an effect' of amylin *in vitro* or *in vivo* is not the issue. Given the breadth of the genus 'SEQ ID NO: 14', it is not possible to envisage what precise structure in the genus of 'SEQ ID NO: 14' provides for the required functionality, i.e., the ability to treat obesity in a generic human subject in need thereof. The specification does not provide adequate guidance with regard to this and does not establish a concrete structure-function relationship. A review of the instant specification indicates that amylin itself has not been shown to be capable of treating obesity in a diabetic or non-diabetic human. See the lack of scope of enablement rejection below at paragraph 37. With regard to the amylin agonist analogue or peptide variant species, the showing in the instant specification is limited to the pramlintide species. Only pramlintide species at specific doses and via specific routes is shown to reduce body weight of a specific human population in need of treatment. However, outside this scope, neither the specification nor the art at the time shows that the amylin agonist analogues or peptide variants having a structure considerably different from that of pramlintide, did retain the obesity-relieving biologic function(s). In other words, the instant specification fails to demonstrate that the peptide variant species or the amylin agonist analogue species having the recited amino acid substitutions or chemical modifications, if administered by one of skill in the art to a diabetic or non-diabetic human subject or a morbidly obese human subject with or without diabetes, by subcutaneous or non-subcutaneous route in the amount range

recited, would elicit a therapeutic effect against obesity. Precisely what structure of the amylin agonist analogue or peptide variant 'SEQ ID NO: 14' genus provides for the recited functionality, i.e., ability to treat obesity in the broad genus of 'human subject in need thereof' is not identified. There is lack of enablement of a representative number of amylin agonist analogue or peptide variant species within the SEQ ID NO: 14 genus, each having the required functional ability to obesity in a representative number of human subject species. As set forth previously, it should be noted that predictability or unpredictability is one of the *Wands* factors for enablement. In the instant application, Applicants have previously acknowledged that obesity is a complex, multifacorial disease that has been the subject of decades of research. Applicants have acknowledged that there are contradictions and confusion in the relevant art. See pages 22 and 23 of Applicants' response filed 09/02/04. Although Example 9 of the instant specification describes the gastric emptying assay and the effect of specific amounts of 'amylin' (as opposed to the amylin agonist analogue SEQ ID NO: 14) on gastric emptying in diabetic rats, and Examples 7 and 8 describe the receptor binding and soleus assays of some amylin variants, of the various biologic activities or functions attributed to amylin or pramlintide, which precise activity or activities provide for, or are associated with obesity relief in the 'human subject' genus has not been precisely identified. Of the various screenable activities, whether one activity, all the activities, or a specific combination of activities, are responsible for the obesity-relief function(s) is neither known in the art nor established within the instant specification, absent which one of skill in the art cannot practice the claimed invention without engaging in a considerable amount of undue experimentation. A mere screening of art-known amylin agonist analogue species falling within the genus of SEQ ID NO: 14 using the conventional screening assays does not enable one to reproducibly practice the claimed method of treatment. Whether or not the various amylin agonist analogue or peptide variant species encompassed within the scope of the SEQ ID NO: 14 genus have the *required* obesity relief function(s) is neither known nor can it be predicted. This is critically important because predictability or unpredictability is one of the *Wands* factors to be considered for enablement. Applicants have previously stated that neither the amylin art nor the obesity art suggested or indicated an approach to trying an amylin or an amylin agonist (let alone an amylin agonist analogue) for weight reduction or treatment of obesity. See bottom of page 57

of Applicants' response filed 09/02/04. With regard to what was known in the art at the time of the invention or thereafter, Applicants stated that Frishman *et al.* ((*In*: *Cardiovascular Pharmacotherapeutics*. (Eds) Frishman WH *et al.* McGraw-Hill Health Professions Division, New York, Chapter 48, pages 1093-1114, February 1997, of record) 'only' concluded that 'the potential role of amylin in weight reduction "awaits clinical investigation"'. See the full paragraph on page 85 of Applicants' response filed 09/02/04. Applicants have recognized the importance of the unpredictability previously. For example, with regard to the gastric emptying function/activity and obesity, Applicants have previously taken the position that there is no agreement on the effect of gastric emptying in obesity. Applicants pointed to various reportings and stated that the role of gastric emptying in obesity was uncertain and controversial at the time of filing of the instant application, as well as before and after. See page 37 of Applicants' response filed 09/02/04. Applicants mentioned of the Minnesota Medical Association's recent reporting that gastric emptying is useful in treating diabetics, but researchers are 'uncertain' whether it will produce weight loss. See page 37 of Applicants' response filed 09/02/04. Applicants have gone on the record previously stating that any and all compounds having any gastric emptying activity are not necessarily useful for treating obesity, let alone one that is being evaluated for use in the treatment of diabetes. See lines 4-6 on page 85 of Applicants' response filed 09/02/04. With the art-known fact that obesity is a complex and multifactorial disease and with the precise amylin or pramlintide activity contributing to obesity relief being unknown at the time of the invention, there is no predictability that the recited peptide variants or amylin agonist analogues having the recited amino acid substitutions or chemical modifications and being encompassed within the genus of SEQ ID NO: 14 would be therapeutically functional as effective obesity-relief agents in a human subject. Furthermore, the effects these various amino acid substitutions and/or chemical modifications would have on the activity of amylin agonist analogues or peptides which contribute to the reported undesired side effects, including recurrent nausea and vomiting and excessive anorexia, and the undesired properties such as insolubility and tendency toward aggregation, are also unpredictable. The various amino acid substitutions and/or chemical modifications encompassed within SEQ ID NO: 4 can potentially render the amylin agonist analogue species or peptide variant species more insoluble than amylin and unacceptably nausea- or vomiting-

inducing. In sum, the instant specification simply lacks a concrete *in vivo* showing that a representative number of amylin agonist analogue or peptide species encompassed within the SEQ ID NO: 14 genus has obesity-relieving function in any human subject in need of the claimed method of treatment. Due to the lack of specific guidance and direction, the lack of evidence and working examples enabling the full scope, the breadth of the claims, the quantity of experimentation necessary, and the art-recognized unpredictability, a considerable amount of undue experimentation would have been required to practice the instant invention. Instant claims clearly do not meet the scope of enablement provision of 35 U.S.C. § 112, first paragraph. The rejection stands.

Double Patenting Rejection(s)

34) Claims 23, 24, 33 and 34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 34 and 35 of the US patent 5,686,411 issued to Gaeta *et al.* ('411, already of record) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract). Although the conflicting claims are not identical, they are not patentably distinct from each other. The method of treatment claimed in claims 34 and 35 of the '411 patent is for the treatment of diabetes mellitus in a mammal comprising the administration to said mammal of a therapeutically effective amount of the amylin agonist of claim 19, ^{25,28,29}Pro-human amylin. The portion of the disclosure of the '411 patent at lines 45-53 in column 7 supporting the limitation mammal does not exclude, but expressly includes a patient seen by a medical practitioner, i.e., a human. The portion of the disclosure of the '411 patent at lines 53-59 in column 8 supporting the limitation 'therapeutically effective amount' of the amylin agonist includes the dosage units of 0.1 to 5 mg or 0.5 to 1.0 mg of the amylin agonist. The amount effective to treat obesity encompassed in the instant claims as described in the instant application, for example, of about 0.01 milligrams to about 5 milligrams per day, about 0.05 milligrams to about 2 milligrams per day, about 0.1 milligrams to about 1 milligram per day, or 300 micrograms per dose, falls in the range disclosed in the '411 patent. The portion of the disclosure of the U.S. patent '411 at lines 9-14 of column 3 describes that the limitation 'diabetes mellitus' includes insulin-requiring diabetes mellitus and that the administration is of amylin agonist analogue *alone*. Given the art-

known prevalence of intrinsic obesity in 80% to 90% of diabetic patients as disclosed by Tsanev, at least 80-90% of the diabetic patients used in the method disclosed in the '411 patent qualify as human patients in need of treatment for obesity. Therefore, the method of the '411 patent comprising the administration of 0.1 to 5 mg, or 0.5 to 1.0 mg of the amylin agonist ^{25,28,29}Pro-human amylin to a diabetic human anticipates the instant claims. Given that the method step of the '411 patent and the instant claims and the amount administered are the same, the method of the '411 patent is expected to bring about a therapeutic effect against intrinsic obesity in the treated diabetic patients as defined in the instant invention, i.e., by controlling weight for cosmetic purposes, or to improve bodily appearance in the diabetic patients.

35) Claims 23 and 33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11 and 13 of US patent 5,321,008 issued to Beumont *et al.* as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract, already of record) and Rink *et al.* (US 5,739,106, already of record) ('106). Although the conflicting claims are not identical, they are not patentably distinct from each other. The limitation 'composition comprising' in claims 23 and 33 does not exclude the presence in the recited composition of a substance such as insulin. The limitation in claim 23: 'said composition is not administered in conjunction with another obesity relief agent' does not exclude the administration in conjunction with insulin. The method claimed in claims 11 and 13 of the US patent 5,321,008 is for the treatment of diabetes mellitus in an insulin-requiring human comprising the administration to said human of a therapeutically effective amount of a calcitonin alone, or calicitonin and insulin. Claim 11 of the '008 patent is directed to the method of administering a therapeutically effective amount of the amylin agonist calcitonin to an insulin-requiring human with diabetes mellitus. The portion of the disclosure of the '008 patent at lines 14-17 in column 5 supporting the limitation 'human' expressly includes a human who suffers from Type 1 or Type 2 diabetes mellitus. The portion of the disclosure of the '008 patent at first full paragraph in column 13 supporting the limitation 'therapeutically effective amount' includes the typical dosage units of about 0.1 to 1 mg of calcitonin. The amount effective to treat obesity encompassed in the instant claims as described in the instant application, for example, about 0.01 milligrams to about 5 milligrams per day, about 0.05 milligrams to about 2 milligrams per day, or 300 micrograms per dose, falls in this range

disclosed in the '008 patent. The portion of the '008 patent that supports the composition in column 12 includes the presence of a pharmaceutically acceptable carrier in the composition and subcutaneous administration. See lines 8-11 and 49-54 in column 12. Given the art-known fact that calcitonin is an amylin agonist as taught at lines 34 and 35 of column 3 of the '008 patent and at line 4 of column 16 of Rink *et al.* ('106), and the art-known prevalence of intrinsic obesity in 80% to 90% of diabetic patients as disclosed by Tsanev, at least 80-90% of the type 2 diabetic patients used in the method disclosed in the '008 patent qualify as human patients in need of treatment for obesity. Therefore, the method of the '008 patent comprising the administration of about 0.1 to 1 mg of calcitonin to a diabetic human anticipates the instant claims. Given that the method step of the '008 patent and the instant claims are the same and the amount administered are the same, the method of the '008 patent is expected to bring about a therapeutic effect against the intrinsic obesity in the treated type 2 diabetic patients as defined in the instant invention, i.e., by controlling weight for cosmetic purposes, or to improve bodily appearance in the diabetic patients.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

36) Claims 23, 33 and 76 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 23, as amended, includes the limitations: 'in need thereof, said method consisting of' comprising administering to said subject an amount of a composition comprising an amylin or an amylin agonist effective to treat obesity wherein the amount of the amylin or amylin agonist administered ..... 'and wherein said composition is not administered in conjunction with another obesity relief agent'. Claim 76, as amended, includes the limitation: 'in need thereof' comprising administering to said subject an amount of a composition comprising ..... 'wherein said amount is effective to treat obesity and wherein said composition is not administered in conjunction with another obesity relief agent'. Claim 33, as amended, 'in need thereof, said method consisting of' administering to said subject 'an amount of a composition effective to treat obesity, said composition comprising an obesity relief agent consisting of an amylin or an amylin agonist and a

pharmaceutically acceptable carrier ....'. Applicants state that the support for the amendment can be found at page 12, lines 13-15 and in the abstract where it is disclosed that the amylin or amylin agonist may be administered alone or in conjunction with another obesity relief agent. However, the abstract of the instant application and lines 13-15 at page 12 of the specification do not describe a method of treating obesity in a human subject in need thereof as claimed wherein 'the composition comprising .... is not' administered in conjunction with another obesity relief agent; or a method of treating obesity in a human subject in need thereof, said method 'consisting of' administering to said subject an amount of a composition effective to treat obesity, said composition comprising an obesity relief agent consisting of an amylin or an amylin agonist and a pharmaceutically acceptable carrier' as recited in the amended claim 33. These parts of the specification make no mention of 'a composition comprising' an amylin or amylin agonist in an amount that is effective to treat obesity wherein said composition is not administered in conjunction with another obesity relief agent, let alone a method 'consisting of' or 'comprising' administering such a composition to a 'human subject in need thereof' to treat obesity. The second paragraph under 'Summary of the Invention' recites that the 'amylin or amylin agonist', as opposed to 'a composition comprising ...', may be administered alone or in conjunction with another obesity relief agent. The originally filed specification describes a statistically significant reduction in the mean baseline weight seen after the subcutaneous administration of an effective amount one specific amylin agonist analogue species, pramlintide, to diabetic subjects for four, 26 or 52 weeks, wherein said pramlintide administration was accompanied with the continued use of insulin. The method as described in the originally filed specification comprised insulin treatment *and* the administration of a specific dose of pramlintide to diabetic patients. This however does not provide descriptive support for the now claimed method of treating obesity in a human in need thereof, said method 'consisting' of administering to said subject an amount of a composition effective to treat obesity, said composition comprising an obesity relief agent consisting of any generic amylin or any amylin agonist and a pharmaceutically acceptable carrier. The scope of the limitation: 'amount of a composition comprising ...' that is effective to treat obesity is not the same as the 'amount of an amylin or amylin agonist' that is effective to treat obesity. The former limitation allows the presence of other element(s) in said composition such as an anti-diabetic agent, insulin, a gastric emptying-inhibiting agent etc. and lacks

descriptive support in the specification, as originally filed. Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P. 608.04 to 608.04(c).

Applicants are invited to point to the descriptive support in specific pages and lines of the disclosure, as originally filed, for the limitation identified above, or remove the new matter from the claim(s). Applicants should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Scope of Enablement)

37) Claims 23, 24, 27, 29, 31-34, 37-39, 80, 82, 95 and 96 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a method of reducing the body weight of an insulin-requiring type II diabetic human subject having a BMI of at least or less than 27 kg/m^2 comprising subcutaneous adjunctive administration to said subject, before each meal three times a day, 30, 75 or 150 micrograms TID of an amylin agonist which is ^{25,28,29}Pro-h-amylin, i.e., pramlintide, for 52 weeks, and a method of reducing the body weight of an insulin-requiring human subject having type 1 diabetes mellitus having a BMI of at least 27 kg/m^2 comprising subcutaneous adjunctive administration to said subject, before each meal four times a day, 30 micrograms of pramlintide for 20 weeks followed by either 30 or 60 micrograms of pramlintide QID up to week 52, of an amylin agonist which is ^{25,28,29}Pro-h-amylin, i.e., pramlintide, wherein said pramlintide is not administered in conjunction with another obesity relief agent, wherein the body weight of said human subject is significantly reduced after 13, 26 and 52 weeks of said treatment compared to the body weight of the placebo group, does not reasonably provide enablement for a method of treating obesity in any human subject including a non-type 2 or non-type 1 diabetic human subject in need thereof, or a type 1 or type 2 diabetic human subject in need thereof who is not on insulin therapy, comprising administering any 'amylin', any 'amylin agonist', or any 'amylin agonist analogue' other than pramlintide by any route other than "subcutaneous" route, and in any amount other than those identified above TID or QID, as

claimed in a broad sense. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Instant claims are evaluated based on *Wands* factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant application, the nature of the invention is treatment of obesity in a human subject in need thereof by administering an amylin, an amylin agonist, or an amylin agonist analogue in an amount effective to treat obesity. As described in the instant specification, the state of the art indicates that obesity or adiposity is a chronic disease that is highly prevalent in modern society, which is strongly associated with multiple conditions including diabetes mellitus, insulin resistance, hypertension etc. The step recited for example in claim 33 'consists of' administering to a human subject in need thereof an amount of a composition comprising a pharmaceutically acceptable carrier and an obesity-relief agent consisting of an amylin, an amylin agonist, or an amylin agonist analogue to treat obesity wherein said amylin or amylin agonist administered is about 0.01 mg to about 5 mg per day. A method of treatment 'consisting of' such an administration step excludes insulin administration simultaneously, or minutes or hours before or after the administration. The method of treating obesity in a human subject in need thereof as claimed in the independent claim 23 'comprises' administering to said subject an amount of a composition comprising a pharmaceutically acceptable carrier and an obesity-relief agent consisting of an amylin or an amylin agonist effective to treat obesity wherein said amylin or amylin agonist administered is about 0.01 mg to about 5 mg per day. The limitation in the claims 'an amount effective to treat obesity' as recited currently is not required to be an amount that is effective to treat obesity --in said human subject in need thereof--,

but encompasses 'an amount effective to treat obesity' in a non-human and a human who is not in need thereof. The limitation 'a human subject in need thereof' encompasses moderately obese, morbidly obese, diabetic and non-diabetic obese, insulin-requiring and insulin non-requiring obese human subject as well as a human subject with age-associated obesity. The limitations "amylin agonist" and "amylin agonist analogue" broadly encompass a myriad of compounds, including a peptide and a nonpeptide compound (see first full paragraph on page 13 of the original specification), non-human amylins, amylins having amino acid modifications or substitutions, and the art-accepted amylin agonists such as calcitonin and CGRP (see lines 45-47 in column 7 of US patent 5,739,106 and claims 3 and 10 of US 5,175,145, both already of record) etc. The breadth of the limitation 'obesity' encompasses non-diabetes-associated obesity, obesity associated with family genetics, morbid and non-morbid obesity, aging-associated obesity, insulin non-treated obesity, obesity due to hypernutrition etc. The limitation 'administering' in the independent claims encompasses administration by any route, i.e., intramuscular, intravenous, oral, intranasal, mucosal, transdermal, topical, transcutaneous etc. and non-mealtime administration, for example, administration 2-3 hours before or after each meal. Example 3 of the instant specification is limited to a demonstration that the human subjects of the study are those with a history of type 2 diabetes mellitus, who require insulin treatment. Body weight-wise, i.e., obesity-wise, these patients are described as having a BMI of at least 27.0 kg/m^2 or less than 27.0 kg/m^2 before admission into the study. The only amylin agonist analogue that was administered in the instant invention was ^{25,28,29}Pro-h-amylin, also known as pramlintide. Groups of type 2 diabetic 'patients' were given separate mealtime pramlintide, 30 micrograms TID; 75 micrograms TID, or 150 micrograms TID subcutaneously before each meal three times a day. Patients *remained on their insulin*, usual diet, and exercise regimens. The study period was 52 weeks, and the outcome was determined by comparing the mean body weight of the treated diabetic subjects with the mean body weight of the placebo subjects. See Tables V-VII. Thus, the originally filed specification at Example 3 and Tables V-VII describes a statistically significant reduction in the mean baseline weight seen after the subcutaneous administration of specific effective amounts of one specific amylin agonist analogue species, pramlintide, three times a day, to type II diabetic subjects for 52 weeks, wherein said pramlintide administration was accompanied with the continued use of insulin. Example 2 of the

instant specification is limited to a demonstration that the human subjects of the study are those with a history of type 1 diabetes mellitus, who require insulin treatment. Body weight-wise, i.e., obesity-wise, these patients are described as having a BMI of at least 27.0 kg/m^2 before admission into the study. The only amylin agonist analogue that was administered in the instant invention was ^{25,28,29}Pro-h-amylin, also known as pramlintide. Groups of type 1 diabetic patients were given subcutaneous adjunctive administration, before each meal four times a day, 30 micrograms of pramlintide for 20 weeks followed by either 30 or 60 micrograms of pramlintide QID up to week 52, of an amylin agonist which is ^{25,28,29}Pro-h-amylin, i.e., pramlintide. See Tables II-IV. Thus, the originally filed specification at Example 2 and Tables II-IV describes a statistically significant reduction in the mean baseline weight seen after the subcutaneous administration of specific effective amounts of one specific amylin agonist analogue species, pramlintide, four times a day, to type I diabetic subjects for 52 weeks, wherein said pramlintide administration was accompanied with the continued use of insulin. There is no showing however that administration of any amount of pramlintide, let alone any other non-pramlintide amylin agonist or amylin itself, administered 1 or 2 times a day did indeed induce obesity relief in diabetic or non-diabetic subjects in need of the treatment. The method as described in the originally filed specification thus comprised insulin treatment *and* the administration of a specific dose of pramlintide in type 1 and 2 diabetic patients. This decrease in body weight was statistically significant compared to the body weight of the placebo subjects. However, the instantly claimed method in not enabled beyond this scope. This is critically important because there is no predictability that if one extrapolated the method of reducing body weight in type 1 or 2 diabetic subjects to non-diabetic obese human subjects, obese subjects not on insulin treatment, or morbidly obese human subjects who are on or not on insulin therapy, the administered amylin, amylin agonist, or amylin agonist analogue including pramlintide, would bring about significant or clinically meaningful weight reducing or obesity-relieving effects. Neither the state of the art at the time of the invention, nor the instant specification as originally filed, provides specific guidance with regard to the use of a generic amylin, or a non-pramlintide amylin agonist, or a non-pramlintide amylin agonist analogue, and its amount that is effective to treat obesity in any human subject in need thereof including an insulin-taking type 1 or 2 diabetic human subject. It should be noted that predictability or unpredictability is one of the *Wands* factors to be

considered for enablement or lack thereof under 35 U.S.C § 112, first paragraph. Amylin, amylin agonists except pramlintide, and pharmaceutically acceptable salts thereof, are not enabled as obesity relief agents in the instantly claimed method. With regard to the therapeutic use of amylin, the state of the art indicates the difficulty, the undesirable pharmacological properties, and the impracticability of using amylin, including human amylin, clinically as 'a therapeutic agent'. For instance, Baron *et al.* (*Current Drug Targets – Immune, Endocrine & Metabolic Disorders* 2(1): 63-82, 2002) taught the following with regard to the clinical use of amylin as a therapeutic agent:

> Clinical use of amylin as a therapeutic agent is considered impractical because of its instability in solution and its propensity to aggregate and adhere to surfaces, properties that hamper the manufacturing, formulation, and storage of this peptide as a drug. Pramlintide is a synthetic, equipotent analogue of human amylin in which the undesirable pharmacological properties of human amylin (insolubility, tendency to self-aggregate) have been overcome by replacement of the three amino acid residues .... with prolines ....

Ratner *et al.* (*Diabetes Technol. Ther.* 4: 51-61, 2002) provide a similar teaching (see paragraph bridging the two columns on page 52):

> Native human amylin is not ideal for clinical use because of the peptide's poor solubility and propensity to aggregate.

Furthermore, with regard to the state of the art at the time of the invention, it should be noted that Applicants have previously argued the following (see pages 9, 13 and 14 of Applicants' Appeal Brief filed July 2000 in the prior application 08/870,762) [Emphasis in original]:

> .... THE RINK PATENT PROVIDES THAT AMYLIN AND AMYLIN AGONISTS ADMINISTERED AS DESCRIBED AND CLAIMED IN THE PRESENT APPLICATION HAVE "NO MEASURABLE EFFECT" ON FOOD INTAKE.
>
> .... the Rink patent reports that a 1.0 μg/kg dose (equivalent to about 70μg/dose in an adult human) had no effect on food intake.

The Rink patent that is being referred to by Applicants in the Appeal Brief is US 5,739,106 (already of record). Applicants have not shown within the instant specification that human or non-human amylin or a composition comprising, consisting of, or consisting essentially of the same, was in fact stable, soluble and/or non-aggregating enough to be therapeutic in a method of treating obesity upon administration in any amount and by any route, with or without concurrent insulin therapy, to a human subject in need thereof. How to determine an amount that is effective to treat obesity of a compound that is recognized in the art to be insoluble and self-aggregating is

not taught. A method of treating obesity in non-diabetic human subjects or subjects not on insulin therapy consisting of or comprising administering an amylin, amylin agonist, or an amylin agonist analogue including pramlintide, or a composition consisting essentially of or comprising of the same, is not enabled. This is important because there is no predictability that if one of skill in the art administered a human or non-human amylin, amylin agonist, or an amylin agonist analogue including pramlintide, or a composition comprising or consisting of the same, to a non-type 1 or 2 diabetic obese human not on insulin therapy, in an amount taught within the instant specification, the administered amylin, amylin agonist, an amylin agonist analogue, or pramlintide, would bring about a therapeutic effect against obesity in said subjects. With specific reference to pramlintide, the state of the art several years after the effective filing date of the instant application, documents that the weight effect of pramlintide in non-insulin treated human subjects is not known. For instance, Hollander *et al.* (*Obesity Res.* 12: 661-668, April 2004) documents the following (see page 666) [Emphasis added]:

> Studies in non-insulin-treated subjects **would allow** examination of the weight effect of pramlintide without the potential confounding effect of changes in insulin use.

The weight reducing or obesity-relieving effect of pramlintide administered alone or as an adjunct to insulin therapy, to a non-diabetic human patient, or the weight reducing or obesity-relieving effect of any amylin, amylin agonist, or amylin agonist analogue, administered alone or as an adjunct to insulin therapy, to an obese diabetic or non-diabetic human subject, is simply not predictable. For the reasons delineated above and due to the lack of specific direction or guidance within the instant specification, the breadth of the claims, the absence of working examples enabling the full scope, the art-recognized unpredictability factor, and the quantity of the experimentation necessary, a considerable amount of undue experimentation would have been required to reproducibly practice the full scope of the invention, as claimed. Instant claims do not meet the scope of enablement provisions of 35 U.S.C. § 112, first paragraph.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

38) Claims 23, 24, 27, 29, 31-34, 37-39, 68, 72, 76, 80, 82, 84 and 95-97 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 23, 33 and 76 are vague and indefinite in the limitation: 'amount effective to treat obesity' because it is unclear in whom the recited amount is effective to treat obesity. For the purpose of distinctly claiming the subject matter, it is suggested that Applicants replace the above-identified limitation with the limitation --amount effective to treat obesity in said human subject--.

(b) Claim 23 is indefinite, internally inconsistent, and/or has confusing antecedent basis in the limitation: 'the amount of the amylin or amylin agonist administered' (see lines 4 and 5). The earlier part of the claim recites that what is administered is 'an amount of a composition'.

(c) Claim 33 is indefinite, internally inconsistent, and/or has confusing antecedent basis in the limitation: 'the amount of said amylin or amylin agonist administered' (see line 5). The earlier part of the claim recites that what is administered is 'an amount of a composition'.

(d) Claims 23 and 43 are indefinite and confusing in the limitation: 'administering ..... a composition comprising amylin or amylin agonist' (see lines 2 and 3) and 'the amylin or amylin agonist administered is'. It is unclear whether what is administered to the recited subject is amylin or amylin agonist, or a composition comprising an amylin or amylin agonist.

(e) Claims 24, 27, 29, 31, 32, 34, 37-39, 68, 72, 80, 82, 84 and 95-97, which depend directly or indirectly from claim 23, 33 or 76, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C § 102

39) Claims 23, 24, 27, 29, 31, 33, 34, 37-39, 80 and 82 are rejected under 35 U.S.C § 102(b) as being anticipated by Kolterman *et al.* (WO 96/40220, already of record) ('220) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract, already of record).

Instant claims are granted the effective filing date of the instant application due to the new matter identified above.

It is noted that the inventorship of the Kolterman ('220) publication (Kolterman, Thompson, and Mullane) is non-identical with the inventorship of the instant application (Duft and Kolterman). Therefore, the publication of Kolterman *et al.* ('220) is proper prior art under 35 U.S.C. § 102(a). See MPEP 2132 III.

It is further noted that the limitation 'treating obesity' is defined in the instant specification as including 'controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance', or preventing 'the onset of symptoms or complications, alleviating the symptoms or complications'. See second paragraph on page 9 of the substitute specification. It is noted that the patient population used in the instant invention to treat obesity by the administration of the recited amount of pramlintide is insulin-requiring Type 2 diabetics. See Example 1 of the instant specification.

Kolterman *et al.* ('220) taught a method of administering to an insulin-taking type II diabetic human subject a dose of 10, 30, 50, 60 or 150 micrograms per day (i.e., the amount falling in the range recited in the instant claims) of the amylin agonist composition, pramlintide or $^{25, 28, 29}$pro-h-amylin, also known as AC137. The composition consists of pramlintide and a pharmaceutically acceptable carrier, and is administered in single or multiple doses, for example, in a dose of about 30 micrograms QID or about 60 micrograms TID or QID. See pages 9-11; paragraph bridging pages 20 and 21; page 21; first paragraph in page 19; lines 8-10 on page 19; and first row reciting 'Insulin-Treated Patients' in each Table. Pramlintide is administered subcutaneously 1-4 times a day before meals (see pages 9 and 22). Kolterman *et al.* ('220) additionally taught that the presence of obesity is a characteristic of 'most patients with Type II diabetes mellitus' (see page 10). Kolterman *et al.* ('220) taught the benefit of obtaining weight loss in Type II diabetic patients by teaching that hyperglycemia associated with Type II diabetes can be reversed or ameliorated by weight loss sufficient to restore the sensitivity of the peripheral tissues to insulin (see pages 7, first paragraph), thus indicating that Type II diabetic patients are in need of weight loss. Thus, the very active step of the instantly claimed method was disclosed and practiced by Kolterman *et al.* ('220) in 1996 in the very same patient population used by Applicants in Example 1 of the instant application. The prior art method is the *same* as the instantly claimed method in terms of the amylin agonist or the amylin agonist analogue (pramlintide), the amylin agonist composition or the amylin agonist analogue composition administered, and the insulin-taking Type II diabetic patient population used; 80-90% of whom are known in the art to be intrinsically obese as taught by Tsanev (see Tsanev's abstract), the subcutaneous route of administration, the dose and the daily frequency of the amylin agonist

administered, and the administration step prior to meals. Given Tsanev's express disclosure that 80 to 90% of type II diabetic patients are intrinsically obese, and given Kolterman's ('220) express teaching that obesity is a characteristic of 'most patients with Type II diabetes mellitus', Kolterman's ('220) method of subcutaneous administration of pramlintide to Type II diabetic patients in an amount that falls within the range recited in the instant claims necessarily serves as the claimed method of treating obesity and therefore anticipates the instantly claimed method. Kolterman's ('220) type II diabetic patients to whom pramlintide composition is administered necessarily qualify as human subjects 'in need thereof' as recited in the instant claims. Since the structural limitations of the instantly claimed method are clearly met by the teachings of Kolterman *et al.* ('220), Kolterman's ('220) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the same therapeutic effect. The Office's position that Kolterman's ('220) method is the same as the Applicants' claimed method is based upon the fact that the method step, the compound administered, the amount of the compound administered, the route by which the compound is administered, and the intrinsically obese diabetic human patient population to which the compound is administered, are the *same* in the two methods. The art-recognized intrinsic obesity being prevalent in 80 to 90% of diabetic patients as disclosed by Tsanev (see abstract), Kolterman's ('220) method of administration of the above-identified therapeutically effective amount of the amylin agonist ^{25,28,29}Pro-human amylin to intrinsically obese type 2 diabetic human subjects anticipates the instant claims. Given that the method step of the Kolterman's ('220) method and the instant claims are the same, Kolterman's ('220) method is expected to bring about a therapeutic effect against the intrinsic obesity in the pramlintide-treated type II diabetic patients as defined in the instant invention, i.e., by controlling body weight for cosmetic purposes, or by improving bodily appearance in the diabetic patients. Since the Office does not have the facilities for examining and comparing Applicants' claimed method with that of the prior art, the burden is on Applicants to show a novel difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594. MPEP 2112 refers to *In re Best* to explain that something which is old does not become patentable upon the discovery of a new property; 'the claiming of a new use, new function or unknown property which is inherently

present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)'. Since the prior art clearly teaches the instantly claimed method, any assertions of specific functional properties attributed to the amylin agonist pramlintide in the claimed method are merely inherent and do not necessarily make the claimed method patentable.

Claims 23, 24, 27, 29, 31, 33, 34, 37-39, 80 and 82 are anticipated by Kolterman *et al.* ('220). The publication of Tsanev is **not** used as a secondary reference in combination with the reference of Kolterman *et al.* ('220), but rather is used to show that every element of the claimed subject matter is disclosed by Kolterman *et al.* ('220), with the unrecited limitation(s) being inherent as evidenced by the state of the art. See *In re Samour* 197 USPQ 1 (CCPA 1978). Tsanev's extrinsic evidence makes clear that the missing descriptive matter, i.e., prevalence of 80-90% of obesity in the diabetic subjects, is necessarily present in the thing described by Kolterman *et al.* ('220).

40) Claims 23, 24, 29, 33, 34 and 38 are rejected under 35 U.S.C § 102(e)(2) as being anticipated by Gaeta *et al.* (US 5,686,411, already of record) ('411) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract, already of record).

The limitation 'method ... comprising ..... wherein said compound is not administered in conjunction with another obesity relief agent' in claim 23, and the limitation 'composition comprising an obesity relief agent .... carrier' in claim 33 do not exclude the presence of an anti-diabetic agent, insulin, glucagon, a gastric emptying-inhibiting agent, etc. in the recited composition.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 C.F.R 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention 'by another', or by an appropriate showing under 37 C.F.R 1.131.

Gaeta *et al.* ('411) taught a method of treatment of diabetes mellitus in a mammal, including a patient seen by a medical practitioner, i.e., a human, comprising the administration to

said mammal of a therapeutically effective amount of the amylin agonist of claim 19, ^{25,28,29}Pro-human amylin. See claims 34, 35 and 19; and lines 45-53 in column 7 of the '411. Gaeta *et al.* ('411) taught the 'therapeutically effective amount' of the amylin agonist to include the dosage units of 0.1 to 5 mg or 0.5 to 1.0 mg of the amylin agonist. See lines 53-59 in column 8. The amount effective to treat obesity encompassed in the instant claims as described in the instant application, for example, about 0.01 milligrams to about 5 milligrams per day, about 0.05 milligrams to about 2 milligrams per day, or 300 micrograms per dose, falls in the range of therapeutically effective amount of the amylin agonist disclosed in the '411 patent. The portion of the disclosure of the U.S. patent '411 at lines 9-14 of column 3 describes that the limitation 'diabetes mellitus' includes insulin-requiring diabetes mellitus and that the administration is of amylin agonist analogue *alone*. The amylin agonist composition comprises a pharmaceutical carrier and the amylin agonist without insulin or glucagon. See lines 9-11 in column 7 and lines 37-39 in column 8. Given the art-known prevalence of intrinsic obesity in 80% to 90% of diabetic patients as disclosed by Tsanev (see abstract), at least 80-90% of the diabetic patients used in the method disclosed in the '411 patent qualify as human patients in need of treatment for obesity. Therefore, the method of the '411 patent comprising the administration of 0.1 to 5 mg, or 0.5 to 1.0 mg of the amylin agonist ^{25,28,29}Pro-human amylin to a diabetic human anticipates the instant claims. Given that the method step of the '411 patent and the instant claims and the amount administered are the same, the method of the '411 patent is expected to bring about a therapeutic effect against intrinsic obesity in Gaeta's ('411) treated diabetic patients as defined in the instant invention, i.e., by controlling weight for cosmetic purposes, or to improve bodily appearance in the diabetic patients.

Claims 23, 24, 29, 33, 34 and 38 are anticipated by Gaeta *et al.* ('411). The publication of Tsanev is **not** used as a secondary reference in combination with the reference of Gaeta *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Gaeta *et al.* with the unrecited limitation(s) being inherent as evidenced by the state of the art. See *In re Samour* 197 USPQ 1 (CCPA 1978). Tsanev's extrinsic evidence makes clear that the missing descriptive matter, i.e., prevalence of 80-90% of obesity in the diabetic subjects, is necessarily present in the thing described by Gaeta *et al.* ('411).

41) Claims 23, 24, 27, 29, 31, 33, 34, 37-39, 80 and 82 are rejected under 35 U.S.C § 102(b) as being anticipated by Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996, already of record) (Kolterman *et al.*, 1996) as evidenced by Itasaka *et al.* (*Psychiatr. Clin. Neurosci.* 54: 340-341, June 2000).

It is noted that a type I diabetic human patient is not excluded from the scope of the instant invention 'as a human subject in need thereof', but is expressly included. See Example 2. It is noted that a 70 kg patient is not excluded from the scope of the instant invention 'as a human subject in need thereof', but is expressly included. The human patient in need of the recited treatment according to the instant invention is expressly identified in the instant specification as one having a body weight of 70 kg. For example, the recited therapeutic amount range of 'about 0.1 milligrams per day to about 1 milligram per day', or 'about 0.01 to about 5 mg/day', or 0.03 to about 5 mg/day of the amylin agonist or amylin agonist analogue, pramlintide, administered is specifically "for a 70 kg patient". See lines 17-23 of page 27 of the instant specification; and lines 7-9 on page 13 of Applicants' response filed December 2002. It is particularly noted that the mean body weight $\pm$ SEM of diabetic patients included in Kolterman's (1996) method who were administered subcutaneously with 30 micrograms, 100 micrograms, and 300 micrograms of pramlintide, three times a day for 14 days, was 70.6 $\pm$ 2.7, 74.4 $\pm$ 2.5, and 75.7 $\pm$ 2.6 respectively. Therefore, the 70.6 to 75.7 kg diabetic patients from Kolterman's (1996) study qualify as 'human subjects in need thereof' as recited in the instant claims.

It is noted that the claimed method of treating obesity in a human subject in need thereof encompasses alleviating the 'symptoms' of the disorder, i.e., obesity. See the last paragraph on page 9 of the substitute specification. The substitute specification at paragraph bridging pages 7 and 8 characterizes 'increased appetite' as a sign strongly associated with obesity (see second paragraph). Thus, increased appetite and therefore, increased food intake is viewed as a 'symptom' of obesity. It is further noted that the limitation 'treating obesity' is defined in the instant specification as including 'controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance', or preventing 'the onset of symptoms or complications, alleviating the symptoms or complications'. See second paragraph on page 9 of the substitute specification. A diabetic human patient having a baseline BMI of up to 27.0 kg/m^2

is not excluded from the scope of the instant invention 'as a human subject in need thereof', but is expressly included. See lines 26 and 27 of page 35 of the instant specification.

Kolterman *et al.* (1996) taught a method of subcutaneous administration of 30, 100, or 300 μg of pramlintide composition or AC137 (i.e., $^{25, 28, 29}$pro-h-amylin), a human amylin analogue, to human patients with insulin-dependent diabetes mellitus or IDDM who are on insulin. Pramlintide is administered three times daily for a period of 14 days. See abstract; and page 493. The mean body weight ± SEM of diabetic patients included in Kolterman's (1996) method who were administered subcutaneously with 30 micrograms, 100 micrograms, and 300 micrograms of pramlintide, three times a day for 14 days before meal, was 70.6 ± 2.7, 74.4 ± 2.5, and 75.7 ± 2.6 respectively. Therefore, the 70.6 to 75.7 kg diabetic patients from Kolterman's (1996) study qualify as 'human subjects in need thereof' as recited in the instant claims. Additionally, even BMI-wise, Kolterman's (1996) diabetic subjects meet the limitation 'human subjects in need thereof' as recited in the instant claims, because the diabetic subjects included in Kolterman's method (1996) had a BMI of up to 27 (see second full paragraph under 'Subjects, materials and methods). Therefore, Kolterman's (1996) diabetic subjects having a BMI at least in the range of 24 up to 27 do qualify as obese diabetic subjects in light of what is known in the art. For example, Itasaka *et al.* teach that a BMI of 24.0 to 26.4 represents mild obesity and 26.4 and heavier (i.e., including a BMI of 26.4 to 27) represents obesity in humans (see abstract of Itasaka *et al*). Kolterman's (1996) pramlintide composition did not comprise another obesity relief agent, but consisted of or consisted essentially of pramlintide. The pramlintide composition was injected subcutaneously to the human patients (see 'Study design') and therefore is expected to inherently contain a pharmaceutically acceptable carrier therein. The amount administered was 30 micrograms three times a day to 'about 0.1 milligrams' or 300 micrograms per day. See 'Study design'; Table 1; and paragraph there below. Kolterman's (1996) subcutaneous administration of a therapeutically effective amount of the amylin agonist ^{25,28,29}Pro-human amylin to diabetic human subjects weighing 70 kg or more, or having a BMI falling in the BMI range of 24 up to 27 anticipates the instant claims. Thus, the very active step recited in the instantly claimed method was disclosed and practiced by Kolterman *et al.* in April, 1996. Given that the method step in Kolterman's (1996) method and the instant claims are the *same* and the amount administered are

the *same*, Kolterman's (1996) method is expected to necessarily bring about the same therapeutic effect in the pramlintide-treated diabetic patients as defined in the instant invention, i.e., by controlling body weight for cosmetic purposes, or by improving bodily appearance in the diabetic patients. Since the Office does not have the facilities for examining and comparing Applicants' claimed method with that of the prior art, the burden is on Applicants to show a novel difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594. MPEP 2112 refers to *In re Best* to explain that something which is old does not become patentable upon the discovery of a new property; 'the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)'. Since the prior art clearly teaches the claimed method, any assertions of specific functional properties attributed to the amylin agonist pramlintide in the claimed method are merely inherent and do not necessarily make the claimed method patentable. Irrespective of the mechanism(s) of action of the amylin agonist pramlintide and irrespective of whether amylin is a peripherally or centrally acting agent, whether or not pramlintide is an anorectogenic agent, gastric emptying-delaying agent, or a food intake suppressing agent, the prior art method of administering the above-explained amount of the amylin agonist ^{25,28,29}Pro-human amylin (pramlintide or SEQ ID NO: 1) to diabetic human subjects weighing 70 kg or more, and/or having a BMI falling in the range of 24 up to 27 necessarily serves as the Applicants' method of treating obesity as defined in the instant application, i.e., 'controlling weight for cosmetic purposes ..., that is to control body weight to improve bodily appearance' in said diabetic human subjects.

Claims 23, 24, 27, 29, 31, 33, 34, 37-39, 80 and 82 are anticipated by Kolterman *et al.* (1996).

42) Claims 23, 24, 27, 29, 33, 34, 37 and 38 are rejected under 35 U.S.C § 102(e)(2) as being anticipated by Beumont *et al.* (US 5,321,008, already of record) ('008) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract, already of record).

It is noted that the limitation 'method ... comprising ..... wherein said compound is not administered in conjunction with another obesity relief agent' in claim 23, and the limitation

'composition comprising an obesity relief agent .... carrier' in claim 33 do not exclude the presence of an anti-diabetic agent, insulin, glucagon, a gastric emptying-inhibiting agent, etc. in the recited composition. It is further noted that 'amylin agonist' is defined in the instant specification as a peptide or non-peptide compound that mimics the effect of amylin. See third paragraph of the specification under 'Summary of the Invention'. Calcitonin and CGRP are described in the instant specification as sharing the food intake-suppressing action or effect of peripherally or centrally administered amylin. See first full paragraph on page 9 of the originally filed specification.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 C.F.R 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention 'by another', or by an appropriate showing under 37 C.F.R 1.131.

Beumont *et al.* ('008) taught a method of treating diabetes mellitus in an insulin-requiring human who suffers from Type 1 or Type 2 diabetes mellitus comprising the subcutaneous administration to said human of a therapeutically effective amount of an amylin agonist *alone* such as calcitonin, or calicitonin and insulin, contained in a pharmaceutically acceptable carrier. See claims 11, 7, 13 and 4; lines 14-17 in column 5; lines 8-11 and 49-54 in column 12; and lines 34 and 35 in column 2. Claim 11 of the '008 patent is directed to the method of administering a therapeutically effective amount of the amylin agonist calcitonin to an insulin-requiring human with diabetes mellitus. The 'therapeutically effective amount' taught by Beumont *et al.* ('008) includes the typical dosage units of about 0.1 to 1 mg of calcitonin. See first full paragraph in column 13. The amount effective to treat obesity encompassed in the instant claims as described in the instant application, for example, of about 0.01 milligrams to about 5 milligrams per day, about 0.05 milligrams to about 2 milligrams per day, or 300 micrograms per dose, falls in the range of the therapeutically effective amount disclosed in the '008 patent. Given the art-known prevalence of intrinsic obesity in 80% to 90% of diabetic patients as disclosed by Tsanev (see abstract), at least 80-90% of the diabetic patients used in the method disclosed in the '008 patent

qualify as human patients in need of treatment for obesity. Therefore, the method of the '008 patent comprising the administration of about 0.1 to 1 mg of calcitonin to diabetic humans anticipates the instant claims. Given that the method step of the '008 patent and the instant claims and the amount administered are the same, the method of the '008 patent is expected to bring about a therapeutic effect against intrinsic obesity in Beumont's treated diabetic patients as defined in the instant invention, i.e., by controlling weight for cosmetic purposes, or to improve bodily appearance in the diabetic patients.

Claims 7, 14 and 16 are anticipated by Beumont *et al.* ('008). The publication of Tsanev is **not** used as a secondary reference in combination with the reference of Beumont *et al.* ('008), but rather is used to show that every element of the claimed subject matter is disclosed by Beumont *et al.* ('008) with the unrecited limitation(s) being inherent as evidenced by the state of the art. See *In re Samour* 197 USPQ 1 (CCPA 1978). Tsanev's extrinsic evidence makes clear that the missing descriptive matter, i.e., prevalence of 80-90% of obesity in the diabetic subjects, is necessarily present in the thing described by Beumont *et al.* ('008).

Relevant Art

43) The art made of record and not currently relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Newgard *et al.* (US 6,110,707, filed 01/17/1997) envisioned providing amylin to a mammal exhibiting pathologic obesity (see lines 41-46 in column 4).
- Kopelman (Editorial. *Internat. J. Obesity* 23: Suppl. 7, S1, 1999) taught the existence of a clear association between obesity and type 2 diabetes. Kopelman taught that the two conditions share many common aetiopathological features and 80% of patients with type 2 diabetes are obese. Kopelman taught that the logical way to address the problem would seem to be via an integrated weight management approach using pharmacotherapy. Kopelman taught that numerous studies have shown that losing 5-10% body weight leads to significant improvements in a wide range of metabolic parameters, thereby reducing the need for anti-diabetic medication. See left column.

Remarks

44) Claims 23, 24, 27, 29, 31-34, 37-39, 68, 72, 76, 80, 82, 84 and 95-97 stand rejected.

45) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. The Fax number for submission of amendments, responses and/or papers is (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

46) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

47) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

February, 2007

S. DEVI, PH.D.
PRIMARY EXAMINER